Return to NINDS Parkinson's Disease Research Web

Biomarkers

Principal Investigator: BURKE, ROBERT E
Grant Number: 2P50NS038370-06
Title: Mechanisms of dopamine neuron degeneration

Abstract: Parkinson's disease (PD) is a prevalent and disabling neurological disease characterized by the progressive loss of motor control due to the degeneration of dopamine (DA) neurons of the substantia nigra. Among neurodegenerative diseases, PD has served as a model for the development of novel therapeutic approaches: administration of neurotransmitter precursors (levodopa), cell implantation, and more recently, deep brain stimulation. As important and effective as these advances have been, they only relieve symptoms; none stop the progression of the disease. In order to develop therapies which halt the progression of the disease, we need to achieve a better understanding of the pathogenesis of DA neuron degeneration. This submission represents a competing continuation application for a Morris K. Udall Parkinson's Disease Research Center of Excellence awarded to Columbia University in 1999. This renewal consists of four projects devoted to a single integrating theme: to understand the molecular and cellular mechanisms of dopamine neuron degeneration. While there are many worthy hypotheses of pathogenesis, the subprojects of this proposal will focus on four major current themes in the pathogenesis of PD, related to the roles of: (1) Abnormal intracellular protein degradation; (2) Inflammatory pathways; (3) Programmed cell death (PCD); and (4) Oxidative injury. In Project 1, Dr Serge Przedborski will evaluate the role of cyclooxygenase 2 (COX2) and cytosolic phospholipase A2 (cPLA2) (Theme 2) in mediating dopamine neuron damage in the MPTP model of PD and in human brain samples. In Project 2, Dr David Sulzer will examine in astrocyte and neuron primary cultures the role of chaperone mediated autophagy in the degradation of proteins implicated in PD (Theme 1) and the effect of these proteins on catecholamine sequestration (Theme 4). In Project 3, Dr Robert Burke will use genetic techniques in animal models to examine the roles of the mixed lineage kinases, Akt and JNK in mediating PCD in dopamine neurons (Theme 3), and he will evaluate the functional role of ER stress in initiating cell death (Theme 1). In Project 4, Dr Lloyd Greene will continue to evaluate the functional role of genes identified in the current funding period by SAGE analysis as upregulated following neurotoxin exposure. He will continue his studies of the role of ER stress-related genes (Theme 1) and genes implicated in PCD (Theme 3) in PC12 cells and primary sympathetic neurons, and in living animal models (the latter in collaboration with Drs Burke and Przedborski). He will also examine these transcripts and their protein products in PD brain. -

Principal Investigator: Chase, Thomas
Grant Number: 5Z01NS002265-28
Title: Pathogenesis And Treatment Of Neurodegenerative Disease

Abstract: Unavailable

Principal Investigator: ELSINGER, CATHERINE L
Grant Number: 1R43NS049705-01
Title: fMRI Evaluation of Parkinson's Disease

Abstract: Parkinson's disease (PD) is a progressive and incurable neurological disease affecting an estimated 4 million people worldwide. Health care costs in the U.S. alone have been estimated in excess of $6B. While many FDA-approved therapeutic interventions (pharmaceutical, surgical and physiological) have become available for the management of the motor and cognitive complications associated with PD, the majority of interventions become less effective over time as the disease progresses. The challenge is to develop more effective and longer lasting treatments that alter the disease course in addition to managing symptoms. Identifying incremental therapeutic efficacy over existing treatments may be hindered by existing clinical outcome measures that suffer from relatively low reliability and sensitivity. The next wave of clinical trials, therefore, will likely require reliable and sensitive biological markers that correlate with clinical outcomes. In Phase I of this project, we propose to test the efficacy of functional magnetic resonance imaging (fMRI), as a biomarker for quantifying a therapeutic response in PD. Phase II will entail the development of a standardized neuroimaging platform based on proprietary technology to be implemented across wide range of MRI scanner platforms. This commercial platform will target academic medical centers, hospitals, and clinics, as well as the pharmaceutical industry, in order to facilitate the evaluation of therapeutic response in PD. -

Principal Investigator: Goldstein, David
Grant Number: 5Z01NS002979-06
Title: Clinical Neurocardiology: Catecholamine Systems In Stress And Disease

Abstract: Unavailable

Principal Investigator: ISACSON, OLE
Grant Number: 5R01NS041263-05
Title: ANTI-INFLAMMATORY THERAPIES NEUROTOXICALLY INDUCED PD

Abstract: A recent large Parkinson's Disease (PD) twin study indicates that environmental and toxic factors play major roles in causing typical PD (Tanner, et. al. JAMA, 1999). Interestingly, neuroinflammation seen in the caudate-putamen is a part of the pathophysiology (Brooks, 1999). The progressive decline of dopamine (DA) terminals seen in idiopathic PD can be closely modeled in Macaca fascicularis by low-dose exposure to the mitochondrial toxin, MPTP, over nine to fourteen months. The investigators demonstrated by PET imaging of DA terminal and MRS that such primates provide a physiological chart of degeneration and appearance of PD signs (Brownell, et. al., Nat. Med., 1998). This data profile enables the design of an experimental paradigm for realistically determining toxicity, neuroinflammation and neuroprotection in idiopathic PD. In this project using the PD primate model, the investigators now propose to examine neuroprotection of the dopaminergic system by anti-inflammatory agents. Based on several studies, they hypothesize that a cyclooxygenase (COX) 1 and 2 inhibitor (indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1-H-indole-3-acetic acid]) can decrease inflammatory reactions caused by MPP+ toxicity and also reduce chronic neurodegenerative processes. In the non-human primate, a slow progressive lesion of the nigrostriatal dopaminergic system follows repeated MPTP treatment. Using PET scanning with a receptor ligand for the peripheral benzodiazepine receptor site (11-C-PK1 1195), preliminary experiments indicate that they can visualize the neuroinflammatory reactions during CNS DA degeneration (as determined by 11-C-CFT). These measurements will be combined with MRI and MRS studies of lactate and choline as in vivo biomarkers for the glial inflammatory and toxic responses of the nigrostriatal system. As a therapy, during and after neurotoxic exposure to MPTP, the investigators will treat the PD primates with a COX I and 2 inhibitor to evaluate anti- inflammatory prevention of onset and continued degeneration. Protection of the dopaminergic system by anti-inflammatory agents would be of tremendous therapeutic value for PD. -

Principal Investigator: JENNINGS, DANNA L
Grant Number: 5R44NS043826-03
Title: An Imageing Marker for Parkinson's Disease

Abstract: The development of disease modifying agents in Parkinson's disease has rapidly expanded the need for in vivo markers for diagnosis and monitoring disease progression. Dopamine transporter (DAT) imaging offers the promise of an objective measure of dopaminergic degeneration allowing for identification of changes in the brain that occur early in the illness, prior to clinical diagnosis. The primary goal of this project is to examine the sensitivity and specificity of DAT imaging using [123I]beta-CIT and SPECT imaging as a diagnostic marker in subjects with suspected PD or PS. We have successfully completed the Phase I pilot study for this project and have utilized these data and experience in designing this Phase II SBIR proposed protocol. The overall study design is to recruit subjects with suspected PD from participating community neurologists and compare the baseline diagnoses of the community neurologists, movement disorders experts and dopamine transporter imaging to a 'gold standard' clinical diagnosis assigned by a movement disorder expert at 12 months follow-up. The DAT imaging diagnosis will be compared to the 'gold standard' clinical diagnosis to determine the sensitivity of [123I]beta-CIT and SPECT imaging as a diagnostic marker in PD and PS. This project is a crucial step to begin to establish [123I]beta-CIT and SPECT imaging as an objective diagnostic biomarker prior to a definitive diagnosis in patients with early parkinsonian symptoms. -

Principal Investigator: RACETTE, BRAD A
Grant Number: 5K23NS043351-03
Title: GENETICS OF PARKINSON DISEASE IN THE AMISH

Abstract: The applicant is a neurologist and movement disorders specialist with three years of post-fellowship, faculty experience involving clinical care, clinical trials, and clinical research into etiologic risk factors for PD including genetic factors. The goal of this career development award is to provide the applicant with comprehensive training in genetic epidemiology through course work, individual tutorials, and practical application of gene mapping techniques to a multi-incident Amish family with Parkinson Disease (PD). PD is a neurodegenerative disorder that produces substantial disability for nearly 1 million people in North America. There is no known cause of the disease in the majority of patients; however, a genetic etiology has been found in a few rare multi-incidence families. Identification of such genes and subsequent determination of the cell biological effects of these mutations will provide important clues to the pathophysiology. Each new mutation discovered adds critical converging evidence about pathophysiological mechanisms common to all to those affected with PD. We have identified 27 members of a large Amish family with clinically typical PD and have excluded known PD genetic mutations. However, we still need to prove that PD is inherited in this pedigree. We will use two different methods to prove that PD in this kindred has a genetic basis. The first approach will assume an autosomal recessive model of inheritance and use genetic marker data provided by CIDR on our subjects to perform homozygosity mapping. A second approach will be to calculate a kinship coefficient to determine if the affected members of the pedigree are "more related" than randomly selected age-matched individuals from the same population. Finally, we will test whether [18]FDOPA PET permits the conversion of some people identified clinically as possible or probable PD in to PET-confirmed PD and thereby functioning as an endophenotype for disease state. This family provides a unique opportunity for the candidate to become a productive independent investigator in genetics of Parkinson Disease and other movements disorders and to develop skills needed for interpretation of [18]FDOPA PET.-

Principal Investigator: ROSS, GEORGE WEBSTER
Grant Number: 2R01NS041265-05
Title: Risk Factors for Pathologic Markers of Parkinson Disease

Abstract: The purpose of this continuation application is to further study two neuropathologic markers of Parkinson's disease (PD), neuronal loss in the substantia niqra (SN) and diminished striatal dopamine levels, in brains of Japanese-American male decedents who were participants in the population based Honolulu Heart Program/Honolulu-Asia Aging Study. These are used as continuous endpoints to identify risk factors utilizing exposure data accumulated prospectively over the past 39 years. Findings include significantly lower SN neuron densities in PD cases compared to controls without PD. Further, duration of PD is highly correlated with SN neuron density. Brains with incidental Lewy bodies have intermediate mean densities. These relationships are strongest for the ventrolateral quadrant. Mid-life risk factors found preliminarily to predict low SN neuron density at death include high total kilocalorie intake, dietary iron and manganese, non-smoking of cigarettes, work on a sugar or pineapple plantation, high body mass index, increased time spent in edentary activity, and (in late life) slowed reaction time. Contrary to expectation, an association of advanced age with deceased SN neuron density was not found. To assess the influence of age with qreater certainty a new Aim is proposed: measurement of SN neuron densities in study subjects dying at a younger age, using archived materials from 160 cohort autopsies done prior to 1991. A second important and unexpected finding is of remarkably low SN neuron densities in the absence of Lewy bodies, but in association with parkinsonian signs, in a subset of the decedents. A second new Aim is proposed to extend investigations of this subset by applying a-synuclein immunohistochemistry to areas of brainstem, limbic regions, cortex, and olfactory bulb. These histopathologic studies will help to determine if the subset of decedents with isolated SN neuron loss represents a prodromal phase of PD, or a pathogenesis not associated with a-synucleinopathy. Continuation will allow accrual of SN neuron density measurements for 800 total autopsies, and 440 striatal dopamine assays. The greater numbers will dramatically enhance statistical power for substantiating risk factors preliminarily identified or suspected. This will also provide opportunity to examine the influence of a wider age range, as well as additional occupational, dietary, medical, constitutional, and environmental exposures on SN neuron density and striatal dopamine levels. -

Principal Investigator: SCHOR, NINA F
Grant Number: 5R01NS041297-03
Title: Antioxidant Strategies for Parkinson's Disease

Abstract: Reactive oxygen species (ROS) have been implicated in the pathogenesis of Parkinson's disease. This suggests that antioxidant strategies may be useful in the treatment and/or prevention of this neurodegenerative disorder. We have developed and implemented two models for the central movement disorder and autonomic peripheral neuropathy, respectively, associated with Parkinson's disease. We propose to use these models to design and test antioxidant strategies we have previously developed for adjunctive use with ROS-generating chemotherapeutic agents. We will further use our studies of the biochemical effects of antioxidant treatment to develop a screening test for new antioxidant agents for use in Parkinson's disease and other ROS-related disorders. Specifically, we propose to test the hypothesis that recycling antioxidants increase expression of p21 wafl/cip1,enhance binding of HIF-1 and CREB to DNA, activate NF-kappaB, prevent ROS-induced morphological apoptosis, and decrease ROS-induced membrane phospholipid and protein nitration in culture models of Parkinson's disease. We will further test recycling antioxidants for their distribution to the CNS and peripheral compartments, and use this information to test CNS-penetrating and non-CNS-penetrating agents for efficacy in the central and autonomic nervous system models, respectively, of Parkinson's disease. Finally, we will test the hypothesis that the magnitude of induced in vitro biochemical change for each drug correlates with the degree of protection from the effects of ROS in the CNS or autonomic model. This latter study will pave the way for development of an in vitro screening test for new antioxidant strategies proposed for use in Parkinson's disease. This application specifically addresses the NINDS agenda for research in Parkinson's disease in its development of in vitro screening tests for putative therapeutic agents in general and antioxidants in particular for this disease, its development of animal models for the clinical aspects of Parkinson's disease, and its potential for further elucidation of the mechanisms of ROS-induced apoptosis in the nervous system.-

Principal Investigator: ZIGMOND, MICHAEL J
Grant Number: 5P50NS019608-20
Title: Neuroprotection and early detection in PD

Abstract: Parkinson's disease (PD) poses a serious threat to the health of a large segment of our society. This is an extensively revised renewal application for a Program Project Grant now in its 18th year. During much of the history of the PPG, we have focused on the compensatory changes that underlie the preclinical phase of PD. That line of investigation will continue, while at the same time we will also add two new foci: first, the development of neuroprotective strategies and, second, the detection of PD it its preclinical phase. Neuroprotection: This will now provide the principal long-term focus of the entire PPG. Our approach derives from recent evidence from our labs indicating that the contralateral motor neglect and loss of DA normally following unilateral damage to the nigrostriatal DA projection can be ameliorated by forced use of the contralateral limb. We hypothesize that forced execution of a motor act that is otherwise compromised by PD is neuroprotective, and that this results from an interaction between the motor act, injury, and concomitant increase in the availability of one or more trophic. We will explore this hypothesis using our 6-hydroxydopamine (6-OHDA) rat model. Our work will involve studies of the role of trophic factors (e.g., GDNF, BDNF, and FGF2), estrogen, and aging, as well as anatomical studies to differentiate between protection, rescue and sprouting (Project 1: M. Zigmond, PI). We also use multineuron recording in awake animals to examine the effect of forced use on the functioning of the basal ganglia more broadly (Project 2, D. Woodward, PI). Compensation: In the past, our studies of compensation have focused our studies on adaptations within the nigrostriatal dopamine (DA) system. Our multineuron recordings will now allow us to explore adjustments within other components of the basal ganglia (Project 2: D. Woodward, PI). Early detection: For neuroprotective strategies to be most effective, it is likely that they must be applied as early in the course of the disease as possible. In this respect, the compensatory changes noted above represent a problem to be overcome through the development of diagnostic tests that can detect PD before the emergence of gross neurological deficits. To do so we will develop a multi-dimensional clinical test battery, using PET imaging as the ultimate criteria for nigrostriatal damage (Project 3, N. Bohnen, PI). We believe that by combining a variety of basic, translational, and clinical approaches we will make significant progress toward the development of a therapeutic approach to PD.-